COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

ECHA accepts no responsibility or liability for the content of this table.

Last data extracted on 15.10.2019

Substance name: 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate; 2,2-bis(acryloyloxymethyl)butyl acrylate; trimethylolpropane triacrylate
CAS number: 15625-89-5
EC number: 239-701-3
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2019	Germany		MemberState	1
Comment received				
In section 7, table 5 of the CLH report the following aspects have been noticed: • The given value for the log Kow is 4.35 at 25°C. According to the information on the EC-HA dissemination site (taken from the registration dossier) the log Kow is 4.35 at 20°C (since this calculated value is based on the substance solubility in octanol which was measured at 20°C). • For some physicochemical endpoints, the given values/results, references and comments do not correspond to the listed property. This applies to the following end-points: o Granulometry (given result: "Stable in organic solvents") o Stability in organic solvents and identity of relevant degradation products (given result: "The substance does not dissociate in water") o Dissociation constant (given result: "122 mPa.s (dynamic) at 20 °C") o Viscosity (given result: "Clear liquid") • In the confidential annex of the CLH report for all given substance compositions the EC No. given for the main constituent TMPTA (table 1 in all sections) is incorrect.				

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2019	Belgium	ReachCentrum PARAD Consortium	Industry or trade association	2
Comment received				
ReachCentrum SA is submitting the comments concerning the CLH Proposal on behalf of the Polymerisable Acrylate Resins and Derivatives REACH Consortium and representing the registrants of 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate; 2,2-bis(acryloyloxymethyl)butyl acrylate; trimethylolpropane triacrylate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TMPTA_PARAD_Comments_PublCons_October 2019.zip				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number

11.10.2019	United Kingdom	Exponent International	Company-Manufacturer	3
Comment received				
Dermal tumours in the Tg.AC mouse are a measure of prolonged irritancy, not intrinsic carcinogenicity. This mouse model is no longer preferred by NTP, the sponsors of the study, due to a high false-positive rate. No dermal tumours were seen in F-344 rats or B6C3F1 mice (normal skin). Additionally, tumours of the forestomach are in a tissue not relevant to human. These tumour incidences, in an inappropriate model, are irrelevant to classification.				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	United Kingdom	Exponent International	Company-Manufacturer	4
Comment received				
Rare liver tumours occur in a strain of mouse (B6C3F1) that gives a high profusion of liver tumours; at least 76% of control females had hepatocellular adenoma and/or carcinoma and at least 26% had multiple liver tumours. In treated groups, the incidence of hepatocellular adenoma and carcinoma were not statistically different to control. A comet assay in mouse liver showed no DNA damage. There is also no evidence of hepatotoxicity. In the TMPTA study, tumours of interest are restricted to females. Hepatoblastoma (HB) in females showed no dose relationship and all HB occurred in individuals that presented with another hepatocellular tumour. HB occurs occasionally in females of this strain but is more common in males. In male controls, the incidence of HB was higher than the mean of the historical control data (HCD), suggesting that the population of mice in this study is susceptible to spontaneous HB. Hepatocholangiocarcinoma (HCC) appears very rare in the female HCD, but in the HCD for males HCC appears to cluster: that is, in the few studies where HCC is reported in controls, multiple animals are affected in the study. The presence of 2 HCC in control males in the TMPTA study suggests the population of mice in this study is susceptible to spontaneous HCC. The high incidence of spontaneous liver tumours in this study makes this study unreliable for the assessment of hepatocarcinogenesis, as noted in the "Guidance on Application of the CLP Criteria". The apparent increases in HB and HCC in this study do not provide reliable evidence for classification. This reasoning is more comprehensively explained in Exponent document 1602127.000-1225 (TMPTA_PARAD-Cons_Full text_Carcinogenicity_October 2019), submitted separately.				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	United Kingdom	Exponent International	Company-Manufacturer	5
Comment received				
Uterine stromal polyp in female mice is a poor indicator of human carcinogenesis; the biology and etiology differ from that of humans (Davis, 2011). Statistical significance might be attributed to a control value below the HCD mean. There is an omission in the CLH report: the incidence of uterine malignant sarcoma is similar in control and high dose animals (a uterine sarcoma of uncertain origin – i.e, uncertain as to if it is of stromal origin - was present in a control animal). Uterine stromal polyp in mice are insufficient basis for classification. Reference: Davis (2011): https://journals.sagepub.com/doi/pdf/10.1177/0192623311431466				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	United States	Exponent International	Company-Manufacturer	6

Comment received

Classification as Carc Cat 2 is not supported. The data for carcinogenicity are peculiar, require careful interpretation, and offer inadequate evidence for classification.
Malignant mesothelioma of the tunica vaginalis (TVM) in the male Fisher-344 rat is highly site-specific and characteristic of this strain of rat. While mesothelium is a tissue lining the thoracic, abdominal and (in males) scrotal cavities, the F-344 shows a pronounced and peculiar susceptibility to mesothelioma specific to the tunica vaginalis. Maronpot et al. (2009, 2016) observes that in NTP F-344 studies where treatment-related TVM are reported, no mesothelioma occurred in females. It should be noted that the application site for TMPTA was between the shoulders; higher exposure might be anticipated in the thoracic, rather than scrotal, cavity. The lack of relevance of F344 rat TVM tumours to humans is discussed by Maronpot et al. (2009, 2016), who postulate an association between TVM and Leydig cell tumours (LCT) in the F-344 rat. The male F-344 rat has a notably high background incidence of LCT, as mentioned in the "Guidance on Application of the CLP Criteria". Although no dose-related change in the incidence of LCT was observed in the TMPTA study, 5 of 6 high dose TVM tumours occurred in individuals that were also identified as having LCT. This peculiarly site- and species-specific TVM in F-344 rats is concluded to be a spurious finding, irrelevant to classification.
The CLH report indicates that the association between TVM and LCT in this study should be dismissed because "Maronpot et al. (2009) concluded on human relevance on the basis of old articles (1992-1997) stating rarity of human Leydig cell tumors. Owing to knowledge gained in the two last decades, the evaluation has changed to-day and needs updating." The TMPTA Consortium is unaware of specific "new knowledge" in this context or how it affects the evaluation. The specific "new knowledge" and a detailed reasoning as to how it affects the evaluation should be specified in the CLH report. Further, Maronpot et al. followed up the 2009 publication with another in 2016 that reaffirms and updates the information presented in the 2009 paper.
References:
Maronpot et al. (2009) Induction of tunica vaginalis mesotheliomas in rats by xenobiotics. Crit Rev Toxicol. 2009;39(6):512-537.
Maronpot et al. (2016):
https://www.tandfonline.com/doi/full/10.1080/10408444.2016.1174669

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2019	Belgium	ReachCentrum PARAD Consortium	Industry or trade association	7

Comment received

The TMPTA Industry Consortium does not support classification as Carc Cat 2, and argues that the data for carcinogenicity are peculiar, require careful interpretation, and offer inadequate evidence for classification.
Dermal tumours in the Tg.AC mouse are a measure of prolonged irritancy, not intrinsic carcinogenicity. This mouse model is no longer preferred by NTP, the sponsors of the study, due to a high false-positive rate. No dermal tumours were seen in F-344 rats or B6C3F1 mice (normal skin). Additionally, tumours of the forestomach are in a tissue not relevant to human.
Malignant mesothelioma of the tunica vaginalis (TVM) in the male Fisher-344 rat is highly

site-specific and characteristic of this strain of rat. While mesothelium is a tissue lining the thoracic, abdominal and (in males) scrotal cavities, the F-344 shows a pronounced and peculiar susceptibility to mesothelioma specific to the tunica vaginalis. It should be noted that the application site for TMPTA was between the shoulders; higher exposure might be anticipated in the thoracic, rather than scrotal, cavity. The lack of relevance of F344 rat TVM tumours to humans is discussed by Maronpot et al. (2009, 2016), who hypothesis an association between TVM and Leydig cell tumours (LCT) in the F-344 rat. The male F-344 rat has a notably high background incidence of LCT, as mentioned in the "Guidance on Application of the CLP Criteria". Although no dose-related change in the incidence of LCT was observed in the TMPTA study, 5 of 6 high dose TVM tumours occurred in individuals that were also identified as having LCT. This peculiarly site- and species-specific TVM in F-344 rats is concluded to be a spurious finding, irrelevant to classification.
The CLH report indicates that the association between TVM and LCT in this study should be dismissed because "Maronpot et al. (2009) concluded on human relevance on the basis of old articles (1992-1997) stating rarity of human Leydig cell tumors. Owing to knowledge gained in the two last decades, the evaluation has changed to-day and needs updating." The TMPTA Consortium is unaware of specific "new knowledge" in this context or how it affects the evaluation. The specific "new knowledge" and a detailed reasoning as to how it affects the evaluation should be specified in the CLH report. Further, Maronpot et al. followed up the 2009 publication with another in 2016 that reaffirms and updates the information presented in the 2009 paper.
Rare liver tumours occur in a strain of mouse (B6C3F1) that gives a high profusion of liver tumours; at least 76% of control females had hepatocellular adenoma and/or carcinoma and at least 26% had multiple liver tumours. In treated groups, the incidence of hepatocellular adenoma and carcinoma were not statistically different to control. There is also no evidence of hepatotoxicity. In the TMPTA study, tumours of interest are restricted to females. Hepatoblastoma (HB) in females showed no dose relationship and all HB occurred in individuals that presented with another hepatocellular tumour. HB occurs occasionally in females of this strain but is more common in males. In male controls, the incidence of HB was higher than the mean of the historical control data (HCD), suggesting that the population of mice in this study is susceptible to spontaneous HB.
Hepatocholangiocarcinoma (HCC) appears very rare in the female HCD, but in the HCD for males HCC appears to cluster: that is, in the few studies where HCC is reported in controls, multiple animals are affected in the study. The presence of 2 HCC in control males in the TMPTA study suggests the population of mice in this study is susceptible to spontaneous HCC. The high incidence of spontaneous liver tumours in this study makes this study unreliable for the assessment of hepatocarcinogenesis, as noted in the "Guidance on Application of the CLP Criteria". The apparent increases in HB and HCC in this study do not provide reliable evidence for classification.
Uterine stromal polyp in female mice is a poor indicator of human carcinogenesis; the biology and etiology differ from that of humans (Davis, 2011). Statistical significance might be attributed to a control value below the HCD mean. There is an omission in the CLH report: the incidence of uterine malignant sarcoma is similar in control and high dose animals (a uterine sarcoma of uncertain origin – i.e, uncertain as to if it is of stromal origin - was present in a control animal).
Overall, the tumour types observed in the TMPTA studies do not provide a reliable or adequate basis for classification. No classification should be applied.
Comments are addressing Sections 10.7 (p19), 10.7.1 (p20), 10.7.2 (p26) and 10.7.3 (p29) of the CLH Proposal

ECHA note – An attachment was submitted with the comment above. Refer to public attachment TMPTA_PARAD_Comments_PublCons_October 2019.zip

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2019	Germany		MemberState	8
Comment received				
Based on the available data the classification for Carc. 2 is supported. Two NTP studies on carcinogenicity were performed. One with rats and mice (2012) and one with transgenic mice (2005). The study from 2012 showed increased incidences of malignant mesothelioma (slightly above the historical control range) in male rats as well as increased incidences of hepatoblastoma (not dose-dependent), hepatocholangiocarcinoma and uterine stromal polyps or stromal sarcoma in female mice after dermal application. There were no neoplastic effects found in female rats and male mice. In this study there was no difference in survival reported but skin reactions such as hyperplasia, hyperkeratosis and chronic in-flammation were found in rats and mice. Transgenic mice showed increased incidences and multiplicity of squamous cell papilloma at the site of application in both sexes and forestom-ach squamous cell papilloma in female mice after dermal application (NTP, 2005). Overall, an increased incidence in malignant and benign tumours was found in female mice and an increased incidence in malignant tumours in male rats after dermal application. Fur-thermore, there is evidence of benign tumours in transgenic mice with one site in males and two sites in females. Although the mode of action is unknown and there was no common target organ identified in the two species and sexes, there is sufficient evidence of carcino-genicity of TMPTA for classification as Carc. 2.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2019	Germany		MemberState	9
Comment received				
Based on the available data the proposal for no classification is supported. Four bacterial reverse mutation assays (OECD TG 471) showed positive results for TA1535 in the presence of metabolic activation in two out of 4 assays but without a dose-dependency. Furthermore, four in vitro mammalian gene mutation assays (OECD TG 476) were reported either using L5178Y mouse lymphoma cells or CHO cells. TMPTA was found to induce gene mutations in mouse lymphoma cells without metabolic activation but not in CHO cells. In the same studies chromosomal aberrations were reported for mouse lymphoma cells and CHO cells as well as increased micronucleus frequencies in mouse lymphoma cells. However, the positive results in these assays were found in the presence of various degrees of cytotoxicity. Positive results were also obtained in an in vitro mammalian chromosome aberration test (OECD TG 473) using human lymphocytes although as above in the presence of cytotoxicity. Furthermore, in vivo assays were reported, namely in vivo micronucleus assay (OECD TG 474) and in vivo mouse alkaline Comet assay (OECD TG 489). The micronucleus assay showed negative results, but the result is questionable as there is no evidence if the target tissue was reached. For the in vivo Comet assay negative results were reported for the liver which is a target tissue of carcinogenicity but increased mean tail intensities were found in the bone marrow although not dose-dependent. However, the validity of the assay was ques-tioned in the dossier as a very short sampling time after treatment and an unusual solvent (PEG 400) which may be influencing the reactivity of TMTPA were used. Overall, there are some limitations to the data presented as positive results in vitro were found in the presence of cytotoxicity or without a dose-dependent effect and the validity				

of the in vivo assays is questionable. Therefore, the data presented are not sufficient for classi-fication.

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2019	Iceland		Individual	10
Comment received				
Comments attached on the Germ Cell Mutagenicity of trimethylolpropane triacrylate (CAS Number: 15625-89-5), pages 10-18 of the CLH report. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on the CLH report for TMPTA final.docx				

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2019	United Kingdom		Individual	11
Comment received				
Attached comments refer to the germ cell mutagenicity section, pages 10-18 of the CLH report. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fowler TMPTA CLH comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2019	Belgium	ReachCentrum PARAD Consortium	Industry or trade association	12
Comment received				
The TMPTA Registrants agree that no classification for mutagenicity is required for TMPTA. The mutagenic, clastogenic, and aneugenic properties of TMPTA were adequately investigated both in vitro and in vivo. In vitro, TMPTA primarily induced clastogenicity, but such an effect was not evident in vivo in OECD test guideline compliant studies. The in vivo comet assay is believed to be a reliable indicator assay for detecting gene mutagens as well as clastogens and this assay was negative with TMPTA. Thus, no data gaps were identified, and the database is sufficient to comprehensively assess the genotoxicity of TMPTA. Based on the available data, it is concluded that although TMPTA is an in vitro clastogen at cytotoxic concentrations, no such activity is likely to occur under normal in vivo conditions because of the cellular protective mechanisms operating in an intact animal. The Comet assay performed on TMPTA followed the OECD Test guideline n°489 (2016) is reliable and conclusive. The study design, required by ECHA, included intravenous treatment of female mice and analyses of liver and bone marrow cells. Based on these Comet results, it was concluded that TMPTA did not induce biologically relevant increases in tail intensity in the liver or bone marrow when treated up to 20 mg/kg/day in female mice, considered as the maximal tolerated dose. Comments are addressing Sections 10.6.1 (p15), 10.6.2 (p17) and 10.6.3 (p18) of the CLH Proposal ECHA note – An attachment was submitted with the comment above. Refer to public attachment TMPTA_PARAD_Comments_PublCons_October 2019.zip				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	Belgium		MemberState	13
Comment received				
The Belgian CA supports the proposed environmental classification of trimethylolpropane triacrylate with: Aquatic Acute 1, H400; M=1 Aquatic Chronic 1, H410; M=1 Degradation Based on the results of a readily biodegradation study, it can be decided that the substance is readily biodegradable (>60% CO2-evolution). Bioaccumulation We agree with the conclusion of the DS. Following the CLP-guidance, for surface-active substances a QSAR estimated value of Kow or an estimate based on individual n-octanol and water solubilities should be provided instead of an analytical determination of Kow. According to the decision scheme in the CLP-guidance, if no valid/high quality experimentally determined BCF value is available and no valid/high quality experimentally determined log Kow, the use of validated QSAR estimations of Log Kow should be used. The CMC-refined (ratio between solubility in octanol and critical micelle conc) log Kow for TMPTA is 4.35, no experimental BCF is available only BCF estimations. Therefore it could be decided on the basis of a Log Kow >4 that the bioaccumulation criterion is not met. Aquatic Toxicity • Acute The most sensitive species in acute toxicity studies is fish with a 96hLC50 of 0.87 mg/L which warrants a classification with Aquatic Acute 1, H400 and M-factor of 1. We question however the reliability of the Daphnia study (Anonymous, 1991) as values are reported as nominal while no analytical monitoring was performed. • Chronic Based on the most stringent outcome of the NOEC (algae) and the surrogate approach (no chronic toxicity data for fish and invertebrates + bioaccumulation potential) the substance should be classified as Aquatic Chronic 1, H410 with M-factor of 1.				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2019	Germany		MemberState	14
Comment received				
We support the proposed classification as Aquatic Acute 1, H400 (M=1) and Aquatic Chronic 1, H410 (M=1). For classification purposes no QSAR estimated BCF values should be used. According to the Guidance on the Application of the CLP Criteria only experimentally determined BCF or log KOW values or QSAR estimated log KOW values should be considered.				

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2019	Belgium	ReachCentrum PARAD Consortium	Industry or trade association	15

Comment received
The Polymerisable Acrylate Resins and Derivatives (PARAD) REACH Consortium do not agree with the arguments in relation to bioaccumulation as presented in the CLH Proposal. The PARAD REACH Consortium, on different grounds, supports the proposed environmental CLH classification of acute hazard category 1, H400 and chronic hazard category 1, H410 (M-factor 1) according to Regulation (EC) No 1272/2008 (CLP) which is identical to registrants' environmental self-classification of TMPTA. Comments are addressing Sections 11.1 (p32) to 11.7 (p37) of the CLH Proposal ECHA note – An attachment was submitted with the comment above. Refer to public attachment TMPTA_PARAD_Comments_PublCons_October 2019.zip

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	United Kingdom		MemberState	16
Comment received				
2,2-bis(acryloyloxymethyl)butyl acrylate; (EC: 239-701-3; CAS: 15625-89-5) We agree with the proposal but note the following points in relation to assessment of bioaccumulation. The CLH report includes a CMC-refined log Kow value of 4.35 calculated as the ratio between the solubility in octanol and the critical micelle concentration. This estimated Kow may be more appropriate than an experimental log Kow value due to the surface active properties of the substance. The DS should provide justification for this calculation method which is only appropriate for specific types of surfactants depending on the charge of the headgroup. The CLP Guidance only refers to the use of experimental and not estimated BCF values. Without assessing the BCF QSARs presented in the CLH report in detail, it is unclear to us whether they are suitable to predict the bioaccumulation of this substance (the influence of the surfactant class and alkyl chain lengths is not discussed). Unless the RAC considers that the justification for this modelled BCF value is appropriate, it may be better to only use the modelled log Kow of 4.35 which meets the criteria for bioaccumulation potential under CLP.				

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2019	Sweden		MemberState	17
Comment received				
p. 35-36 Acute aquatic hazard: The reported LC50 (96h) from the acute fish toxicity study (Danio rerio; Anonymous (2016)) is 0.87 mg/L based on measured concentrations. Could you please clarify how this LC50 was derived? Based on the information available, we do not come to the same conclusion considering this LC50. The information found considering this study is compiled in a table in an attachment to this comment. Based on this information, there is 0% mortality at 0.89 mg/L (measured concentration). It is therefore unclear how LC50 (96h) could be set to 0.87 mg/L. If the LC50 (96h) of 0.87 mg/L for fish is incorrect, the proposal for environmental				

classification (acute and chronic) needs to be reconsidered.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment COM_CLH_PC_TMPTA_SE_attachment.docx

PUBLIC ATTACHMENTS
1. TMPTA_PARAD_Comments_PublCons_October 2019.zip [Please refer to comment No. 2, 7, 12, 15]
2. COM_CLH_PC_TMPTA_SE_attachment.docx [Please refer to comment No. 17]
3. Fowler TMPTA CLH comments.pdf [Please refer to comment No. 11]
4. Comments on the CLH report for TMPTA final.docx [Please refer to comment No. 10]